CORRELATION OF SERUM TNF- ALPHA AND IL-6 LEVEL WITH ANGIOGRAPHIC SEVERITY OF CORONARY ARTERY DISEASE

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CERTIFICATE

This is to that the dissertation entitled "**CORRELATION OF SERUM TNF- ALPHA AND IL-6 LEVEL WITH ANGIOGRAPHIC SEVERITY OF CORONARY ARTERY DISEASE"** is the bonafide original work of **Dr. A. RUDRAPPA** in partial fulfillment of the requirements for D.M. Branch-II (CARDIOLOGY) examination of THE TAMILNADU DR. M.G.R.MEDICAL UNIVERSITY to be held in August 2013. The period of post- graduate study and training was from August 2010 to July 2013

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DECLARATION

I Dr. **A. RUDRAPPA**, solemnly declare that this dissertation entitled "**CORRELATION OF SERUM TNF- ALPHA AND IL-6 LEVEL WITH ANGIOGRAPHIC SEVERITY OF CORONARY ARTERY DISEASE**" is bonafide work done by me at the Department of Cardiology, Madras Medical College and Rajiv Gandhi Government General Hospital during the period 2010-2013 under the guidance and supervision of the Professor and Head of the department of Cardiology of Madras Medical College and Rajiv Gandhi Government General Hospital , **Prof. Dr. V. E. DHANDAPANI., D.M.** This dissertation is submitted to The Tamil Nadu Dr. M.G.R Medical University, towards partial fulfillment of requirement for the award of D. M. Degree (Branch-II) in Cardiology.

Place: Chennai **Dr. A. RUDRAPPA**

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INTRODUCTION

Over the last decade, cardiovascular diseases have become the major cause of mortality Worldwide. The south Asian region, one of the world's most densely populated regions, comprises about 20% of the world's population,

The Worlds 20% of the population live in south Asian zone and the density of the population is very high. Being India, largest county in this area, having more than 3 crores of CAD patients. More than 30% of the total population lives in the urban areas this is expected to increase to more than 40% in the next decade. The incidence and prevalence steadily increasing from seven percentage in early 90s to ten percentage in the turn of the millennium. The rural people once thought to be protected from CAD are no longer true. More than half of the CV deaths occur in people less than 70 yrs which create a social burden on our country.

Almost all coronary heart disease results from coronary atherosclerosis. Atherosclerosis is the leading cause of morbidity and mortality throughout the Globe. In acute coronary artery disease generally with superimposed coronary thrombosis. Non-atherogenic forms of coronary artery disease are less common. During the natural evolution of atherosclerotic plaques, especially lipid-laden

plaques, an abrupt and catastrophic transition can occur, characterized by plaque disruption. The last couple of years have witnessed a sea change in the field of atherosclerosis both in terms of enhanced understanding and in the availability of rich panoply of therapeutic options.

Going down the memory lane of atherosclerosis we see that,

In 70s, Atherosclerosis was considered to be a relentlessly progressive disease with no control whatsoever over it and arresting the progress of atherosclerosis or its regression was considered a myth and the idea was totally mooted out.

In 80s, Things changed a little and there was silence over this issue.

In the 90s, the answer to the above issue was perhaps “yes”.

From the year 2000 onwards, modulation of atherosclerosis has become a reality and we can assess the components of atherosclerosis i.e. Lumen of the vessels (coronary angiography and CT- angiography, Angioscopy), Plaque morphology (vascular MRI, IVUS, OCT), Inflammation (intravascular Thermography, FDG, PET imaging, Biochemical markers) over the last fifteen years. However, a prominent role for inflammation in the pathogenesis of atherosclerosis has been established (Libby et al., 2002), the concept that inflammation governs atherosclerosis and its complication has provided a new

unifying hypothesis of the link between risk factors and the cellular and molecular alterations that underlie this disease (Libby and rider, 2006).the hallmark of the early atherosclerotic lesions is the cholesterol ester-laden macrophage foam cell (ross, 1995). Progressive free cholesterol loading of lesional macrophages leads to a series of Phospholipid-related adaptive responses. These adaptive responses eventually fail, leading to macrophage death which further can lead to lesional necrosis, release of cellular proteases, inflammatory cytokines, and adipokines and prothrombotic molecules. These could contribute to plaque instability, plaque rupture, and acute thrombotic vascular occlusion (Tabas, 1997). One such inflammatory markers, serum IL-6 and TNF alpha levels which has come under increasing examination over past ten years or genetics and in particular, the genes involved in the regulation of serum IL-6 and TNF alpha levels within the body. Hence, the present study focuses on the role of serum IL-6 and TNF alpha levels and their association with CVD.

AIM OF THE STUDY

1. To determine the relationship of serum TNF alpha values and Interleukin 6 with coronary artery disease.

2. To determine the relationship of serum TNF alpha and serum Interleukin 6 values with angiographic severity of coronary artery disease

Review of literature

The immune system: cytokines and their function

The effective immunity is due to the interaction of multiple cell types including myeloid cells and lymphocytes. The complex interactions among these cells are in part mediated by cytokines. Cytokines are relatively small regulatory proteins that are secreted from cells of innate and adaptive immunity as well as various other cell types in response to a number of stimuli. On one hand, a subgroup of these proteins stimulate the growth and differentiation of various cells during immune homeostasis, while on the other hand, cytokines facilitate the activation and differentiation of effector cells both during the natural and acquired phases of immunity against foreign antigens such as bacteria, viruses or self-antigens. Binding of cytokines to specific receptors on the membrane of target cells leads to the activation of diverse signal-transduction pathways which ultimately lead to altered gene expression.

In recent years cytokines and their receptors have become important targets for specific antagonists in various immune and inflammatory diseases. One of these

cytokines that is considered as such a target, due to its pro-inflammatory functions is the cytokine Interleukin-6. It is involved in the regulation of immunity, hematopoiesis, bone metabolism and inflammatory state. The increase in Interleukin-6 seen implicated in the pathology of connective tissue and autoimmune conditions and also in coronary artery disease, RA, Crohn's, Castleman's disease and JRA. So IL-6 pathway modulation has become an interesting target for the therapy of above conditions.

The discovery of Interleukin-6

The history of nomenclature reflects the diverse biological functions of this cytokine: Interleukin was initially found to be T cell-derived factor which induces B-cell to produce antibodies. It was first termed B cell stimulatory factor-2. Complementary DNA was later cloned.

Interleukin 6 expression and structure

The human Interleukin 6 gene contains four introns and four exons and maps to chromosome 7p21. Interleukin 6 has molecular weight ranging from 21 – 28 kilo Dalton. Murine IL 6 and Human IL 6 have 65% similarity at their DNA level. IL-6 is not constitutively expressed in the human body, but is induced by a large number of multiple stimuli including bacterial and viral infections, microbial

components such as lipopolysaccharide (LPS) and different cytokines (11). IL-1β, TNF-α and IFN-γ are potent inducers of Interleukin 6 expression in various cells like T cell, B cell, various tumor cells, monocyte, endothelial cell and fibroblasts.

Interleukin-6 promoter

IL6 gene is regulated by a series of transcription factors. Depending on the extracellular stimuli and cell type their interactions differ. So far, several functional cis-regulatory elements in the human IL-6 promoter have been identified, including nuclear factor-kappa B (NF-κB) (position -62 to –49 relative to the translational start codon), nuclear factor-IL6 (NF-IL6) (-144 to -132), cAMP response element binding protein (CREB) (-152 to -145) and activator protein-1 binding sites.

The Rel family of transcription factors includes NF-κB. IκBs (Inhibitors of κB) inhibit NF-κB in resting state. Upon activation of cells by diverse stimuli, IκBs become phosphorylated and are rapidly degraded. The degraded IκBs can no longer bind to NF-κB which is therefore released. It translocates into the nucleus which binds specific DNA recognition site, contributing transcriptional activation of multiple genes.

A low level of NF-IL6 is seen in primary cells. TNF-α, IL-1β or LPS strongly stimulate NF-IL6 expression. In contrast, NF-IL6 is constitutively

expressed in many cell lines. Phosphorylation of NF-IL6 has been shown to increase its transcriptional activity.

Studies in various cell types have shown that induction of IL-6 gene transcription is complex and involves the coordinated regulation of factors that associate with the evolutionary conserved NF-κB, NF-IL6 and AP-1 sites in the mouse and human IL-6 promoter.

Cellular signaling and regulation of Interleukin-6

Receptors of IL 6 are unique. The IL-6 receptor has a 80 kilo Dalton protein which binds to interleukin 6 and another 130 kilo Dalton protein which functions as a transducer of signals.

The 80 kilo Dalton IL-6 receptor can exist as soluble or transmembrane form.

Transmembrane type

It has got intracytoplasmic - 82 aminoacids

It lacks tyrosine-kinase domains

No enzymatic role in IL-6 signaling

When IL-6 binds to its membranous receptor, it brings both intracellular segments in two IL-6R chains with close proximity, thus permitting the attachment of intracellular IL-6R segments with 130 kilo Dalton g-protein. This is found to

induce formation of a multimer consisting of two Interleukin 6 bound to the intracytoplasmatic segments of the two IL-6R proteins.

On the other hand, the soluble form of IL-6R, which is produced by cleavage of the membranous IL-6R or by alternative splicing, can bind IL-6. Two IL-6 molecules, two soluble IL-6R proteins and two gp130 proteins bind together to form a complex. This is able to transmit signals via *trans*-signaling. Gp130 protein dimerization induces activation of JAK tyrosine protein kinase family. The JAK kinase family consists four non-receptor tyrosine kinase members. They are Tyk2, JAK1, JAK, and JAK3 which selectively phosphor late the signal transducer and activator of transcription (STAT) proteins thus leading to their activation. STAT3 phosphorylation is induced by JAKs by translocating inside nucleus in its phosphorylated form and induces gene expression.

Overproduction of IL-6 leads to inflammation and disease; therefore this cytokine must be regulated to control the duration and magnitude of IL-6 response. A negative feed-back loop regulates the IL-6 signaling system via activation of SOCS (suppressors of cytokine signaling) and PIAS (Inhibitors of activated STATs). Phosphorylated STAT3 translocates inside nucleus which induces expression of SOCS3, which binds to JAKs and thus suppresses transduction of GP 130 protein. STAT proteins are negatively regulated by PIAS. In the case of IL-6

signaling, PIAS3 associates specifically with activated STAT3 blocking further gene transcription.

Interleukin-6 and its Biological effects

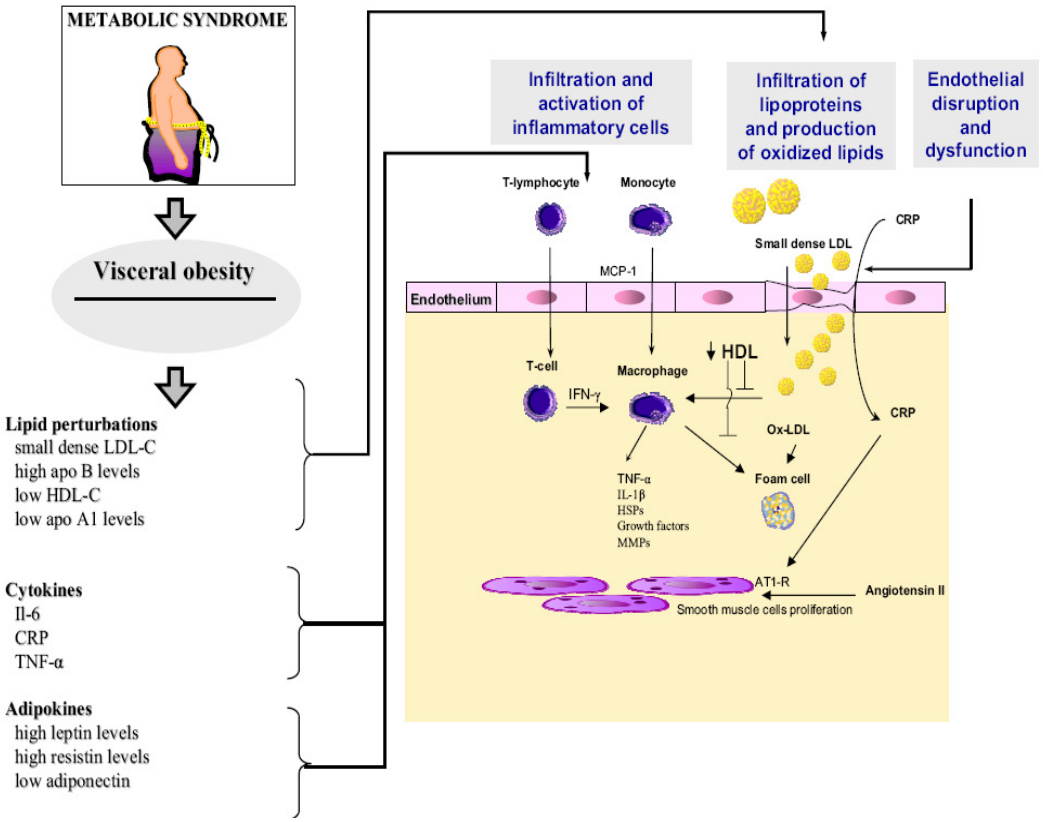
Initial description of IL-6 was a B-cell differentiation factor. Further studies showed that production of Immunoglubulins from B cells is enhanced by Interleukin 6.

Exposure to anti-IL-6 antibody to B-cell causes decreased production of immunoglobulin but does not affects their proliferation. IL-6 is thought to be important factor for production of antibodies by activated B-cell, unaffecting their proliferation. Later on IL 6 was found to have diverse functions on multiple cell types. T cell activation by IL 6 induces production of IL 2 and expression of its receptor. Moreover cytotoxic T-cells formation is brought about by conjugation of IL 6 with IL 2. Furthermore, Interleukin 6 acts as a terminal differentiation factor for macrophages.

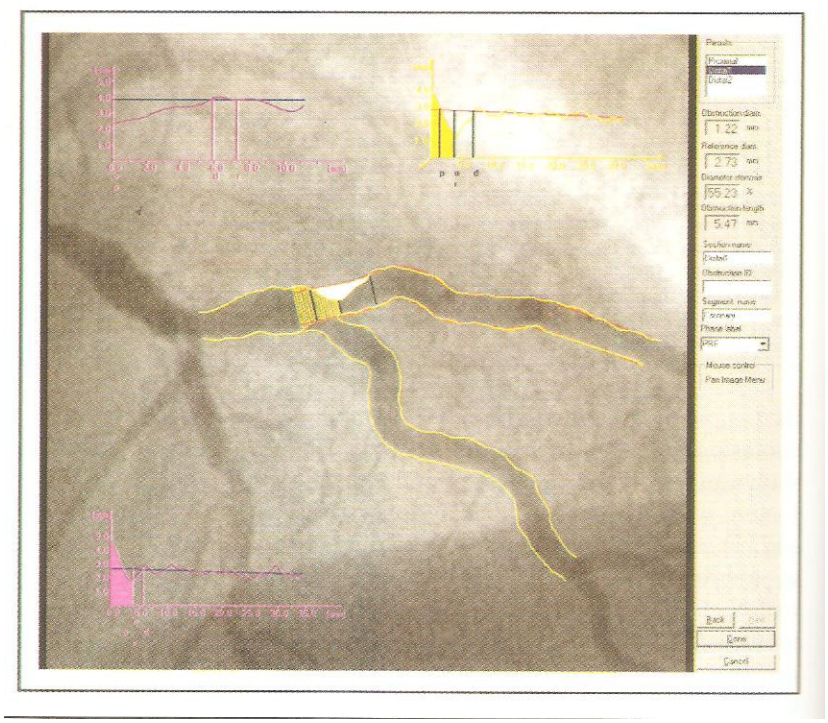
In response to inflammatory signals, Liver cells trigger acute phase response by reduced production of Albumin and increased production of Haptoglobulin, CRP, Serum Amyloid A, Alpha 1 antitypsin and Fibrinogen, which is triggered by IL-6 in response to tissue injury. This is confirmed by various studies in Human hepatocytes. IL 6 considered as a major inflammatory mediator triggering acute

phase response. Along with IL 3, it also induces production of multilineage precursor cell types. Soluble Interleukin 6 receptor is involved in bone metabolism by triggering osteoclast differentiation. Furthermore, IL-6 acts on the differentiation of megakaryocytes to produce platelets and has been shown to support the survival of cultured cholinergic neurons.

Process of early Atherosclerosis



Process of early Atherosclerosis



Hence the following study designed to find the correlation between Serum TNF alpha & Interleukin 6 levels in correlation with coronary artery disease severity.

MATERIALS AND METHODS

METHODOLOGY

This chapter deals with the research approach and design, setting of the study , variables , population, sample size, sampling technique, Sample selection criteria, development and description of the tool, scoring procedure, procedure for data collection and plan for data analysis.

RESEARCH APPROACH AND DESIGN

The approach chosen for the study is cross sectional analysis correlating severity of coronary angiography with increased serum values of TNF alpha, Interleukin 6 in CAD patients. Fasting Serum samples of TNF alpha, IL 6, Lipids, Blood glucose were taken on the day of coronary angiography. Patient's past medical history including any drug intake was obtained and clinical examination was done.

SETTING OF THE STUDY

The study was carried out at the Madras Medical College and Hospital, in Chennai. Madras Medical College is Government Medical College attached Hospital, which runs Inpatient and outpatient services.

VARIABLES

The variables in the study are the demographic variables, BMI, Blood pressure recordings, Fasting Sugar levels, Lipid Profile, serum IL-6 and TNF alpha levels and Coronary Angiography. The severity of coronary artery disease measured with standardized coronary angiographic technique (QUA)-Gensini score.

POPULATION

This study included 122 Adults undergoing diagnostic CAG at Madras Medical College and Hospital. Coronary Angiogram was done in the Cath lab of

the department of Cardiology, Madras Medical College and Hospital. Control group persons without coronary artery disease are selected for serum IL-6 and TNF alpha levels measurement without coronary angiogram.

SAMPLING TECHNIQUE

Non probability convenient sampling technique was used for sample selection based on the inclusive and exclusive criteria.

INCLUSION CRITERIA

All patients of ischemic heart diseases admitted for CAG in department of cardiology, Madras Medical College Hospital.

EXCLUSION CRITERIA

1. Patients with past history of Coronary Artery Bypass Grafting.

2. Patients who had undergone PTCA.

3. Patients with Valvular heart disease.

4. Patients with Hepatic dysfunction.

5. Patients with a major non-cardiovascular disease.

6. Patients with Collagen vascular diseases.

7. Any Systemic Infection.

8. Patients with history of coronary angiography in the recent past.

9. unwilling to give consent.

Using the above criteria those with uncomplicated Acute STEMI were lysed using streptokinase, underwent coronary angiography in 2 to 4 weeks. Control patients group with Acute STEMI with post infarction angina, unstable angina, NSTEMI and chronic stable angina were subjected for coronary angiography.

122 cases were elected for inclusion in the study based on clinical assessment and laboratory screening. An informed consent was obtained from each patient before inclusion in the study. Patient's age, gender, co-morbid conditions, smoking history, BMI, Blood pressure recordings, Weight, Height, Waist: Hip Ratio, heart rate and medication history were noted. Fasting Serum concentrations of glucose, creatinine, urea and lipid profile were measured using standard laboratory procedures.

Systemic Hypertension defined as systolic BP > 140 mmHg and diastolic BP > 90 mm Hg in various postures. Diabetes mellitus being defined by fasting sugar

> 126 mg/dl on two occasions, or patients already on OHA or on insulin. Hypercholesterolemia defined by total cholesterol > 200 mg/dl or LDL-C > 130mg/dl, or as patients already on Statin treatment.

Fasting blood samples of the participants were collected at the day of angiography and sent for analysis of serum IL-6 and TNF alpha levels.

DETERMINATION OF Interleukin 6 and TNF alpha

Serum Interleukin 6 and TNF alpha levels are quantitatively determined on patient's serum by enzyme immunoassay method.

DETERMINATION OF IL-6

IL-6 was quantitatively determined in patient's serum by enzyme linked immunosorbent assay method. The assay employs an antibody specific for human IL-6 coated on a 96-well plate. Standards, samples and biotinylated anti-human IL-6 are pipetted into the wells and by the biotinylated IL-6 specific detection antibody. After washing away unbound biotinylated antibody, HRP-conjugated streptavidin is pipetted to the wells. The wells are again washed. Following this second wash step, TMB substrate solution is added to the wells, resulting in color

development proportional to the amount of IL-6 bound. The stop solution changes the colour from blue to yellow, and the intensity of the color is measured at 450nm.

ECHOCARDIOGRAPHIC DATA

Two dimensional and M-mode measurements were obtained with patients in left lateral position using a Philips HD7 phased array system equipped with tissue Doppler and harmonic imaging technology with Doppler frequency of 2.5 to 3.8 MHZ. With measurement of LV EDD in diastole and LV ESD in systole, LV EF was measured by Teicholtz method.

CORONARY ANGIOGRAPHIC DATA

Coronary angiogram was done in the Toshiba Cath lab in our hospital. CAG was done through Radial or femoral approach.

Coronary angiograms were done through radial or femoral approach using modified Seldinger technique after getting patients and patient's relatives consent. CAG was done with minimum 4 views of LCA and 2 views of RCA. Low osmolar nonionic contrast agent was used. Coronary artery stenosis was evaluated by use

of multiple projections quantitative analysis was done with medical imaging system CMS analysis software.

DETERMINATION OF CAD SEVERITY

Following coronary angiogram, the degree of narrowing was assessed by taking into account the maximum narrowing of each stenotic lesion in at least two orthogonal views. The severity of CAD was evaluated by the 0 to3 vessel disease score, Gensini and ACC/AHA scores.

In the clinical 0 to 3 vessel disease scoring system arteries were as being involved if more than 50% luminal diameter narrowing occurred, and the patients were defined as having 0-,1-,2-,3 vessel disease according to the number of vessels involved.

The 3 coronary scoring systems are described

LEAMAN SCORE

Coronary artery score equals the sum of all segment scores (each segment score equals coronary segment value multiplied by a weighting factor). Weighting factors assigned to the specific percentage luminal diameter reduction of the coronary artery segment are 5 for 100%, 3 for 90-99%,and 1 for70-89%.here we are not using this scoring system .we are using commonly using scoring system

GENSINI SCORE

The Gensini scoring system is a valuable aid to estimate the severity of CAD according to angiographic findings. The calculation is based on the evaluation of number of stenotic segments along with their respective degrees of luminal narrowing and localization within the coronary tree.

The above scoring system is to grade severity of CAD in CAG

Score 1 – 1 - 25%

Score 2 – 26 - 50%

Score 4 – 51 - 75%

Score 8 – 76 - 90%

Score 16 – 91- 99%

Score 32 – 100 % Block

After calculating the score it is multiplied by location of the occluded plaque to corresponding artery

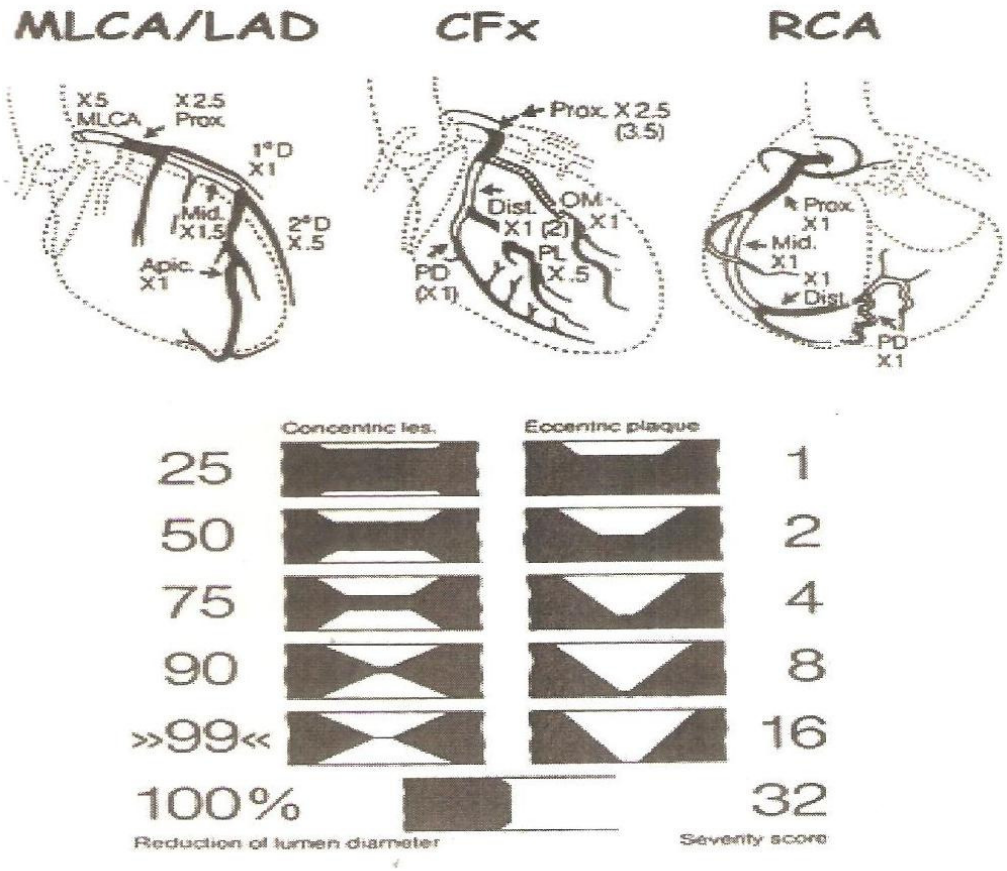
5 – LMCA

2.5 – LAD before D1 & S1, LCX

1.5 – Mid LAD

1 – Distal LAD / Distal LCX / Entire RCA

0.5 – D2/ PLB



The above scoring system takes into consideration of the following factors in calculating the score – location of the plaque and in which artery the plaque present mainly in left system or the right system.

American College of Cardiology / American Heart Association scoring system

CAD scoring system calculated by adding scores from all segments of coronary artery. The scoring given for each lesion based on luminal narrowing.

Score 0 – Less than 10%

Score 1 – 10 to 49%

Score 2 – 50 to 74%

Score 3 – 75 to 89%

Score 4 – 90 to 100%

The branches of LAD or LCX like Diagonals, OMs, Septals and distal LAD with adequate diameter greater than any other branches have been added to the scoring value.

Two Cardiologists calculated the Coronary stenosis severity approved by Professor of Cardiology, Madras Medical College and Hospital.

In contrary to the other scoring systems like Gensini & Leaman, the above scoring pattern give equal weightage to all the segments involved even though they vary in their size and blood flow.

DEVELOPMENT AND DESCRIPTION OF THE TOOL

With the researcher's personal and professional experience and after extensive review of literature and discussion with experts, a structured interview schedule was developed for data collection of the study. For convenience of data collection procedure the tool was translated into Tamil.

Structured Interview schedule

This consist of 2 sections

Section –I

Demographic data regarding patients age, sex.

Section –II

Interview schedule to assess the information need of study.

PROCEDURE FOR DATA COLLECTION

Data collection for the study was done at Department of Cardiology, Madras Medical College & Hospital Chennai, after obtaining necessary permission from the authorities. The data was collected after a brief introduction about self and the study's purpose and after obtaining the written consent of the significant family members of Cardiac Patients.

Data encoding and data analysis.

The collected data were coded in Spreadsheet (Excel) format. Specific codes were developed that were compatible with the subsequent statistical analysis. The coded data were then analyzed with Windows SPSS software (Version 17.0). The results of the analysis were tabulated and inference made from these tabulations.

STATISTICAL ANALYSIS

The patient data is analyzed by standard statistical methods. Variables are depicted as Mean ± S D, Frequencies, Percentages.

The student t test and another method of Analysis of Variance have been used to compare continuous variables.

The correlation was done by multiple linear regression and linear regression.

P values calculated and regarded significant when the value is less than 0.05

RESULTS AND DATA ANALYSIS

This chapter deals with the analysis and interpretations of data collected from 122 significant family members of cardio patients at Dept. of Cardiology, Madras Medical College and Hospital, Chennai to assess the informational need on the study. Data collected from 103 normal persons without coronary angiogram from medical camps.

Table-1

Age distribution of the Sample

Age Group	Male		Female		Total	
	No of Patient	%	No of Patients	%	No of Patients	%
< 30	1	00.99	1	04.76	2	01.63
31- 40	15	14.85	3	14.29	18	14.75
41 -50	37	36.63	8	38.10	45	36.88
51 – 60	38	37.62	8	38.10	46	37.70
61 – 70	10	09.90	1	04.76	11	9.01
Total	101	100	21	100	122	100
Mean ± S d	**50.14 ± 9.00**		**48.57 ± 9.84**		**49.87 ± 9.13**	
	t=0.71 df=120 Not Significant					

Patients were distributed across the age group of 30 to 70 years. Mean age of the patients was **49.87 ± 9.13** years. (Male=50.14 ± 9.00 & Female = 48.57 ± 9.84**).** Most patients (n=46) were in the age group of 51-60 years. Youngest patient

was 23 years old and oldest was 67 years. There is no significant difference was found between male and female age.

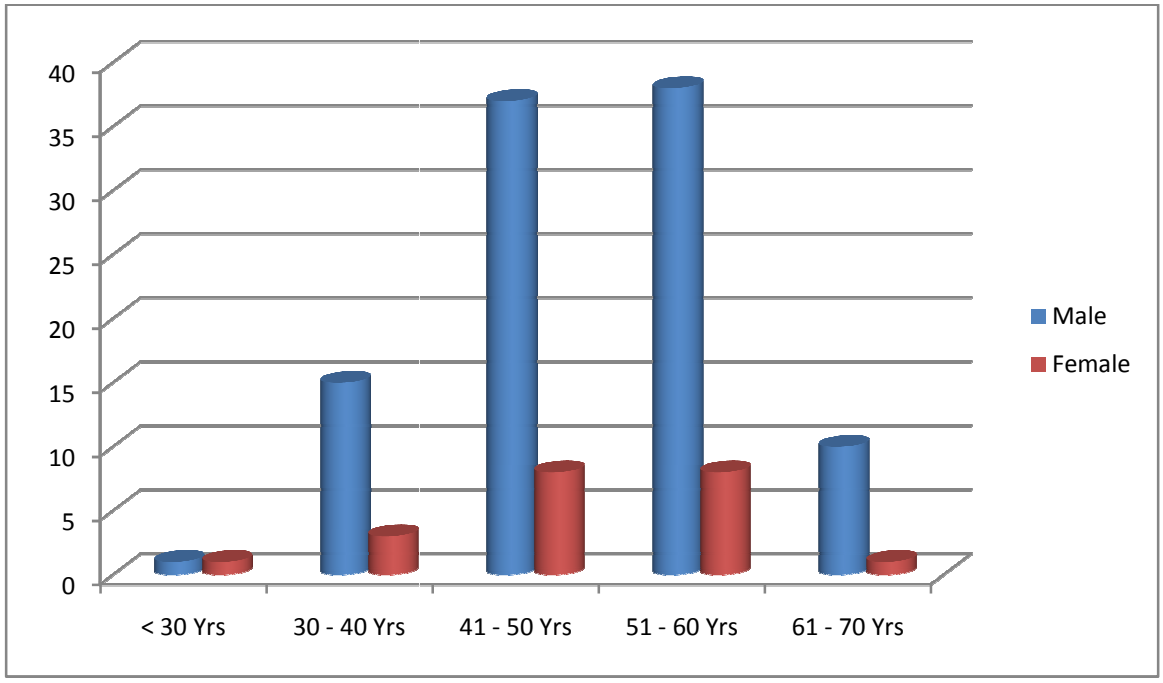
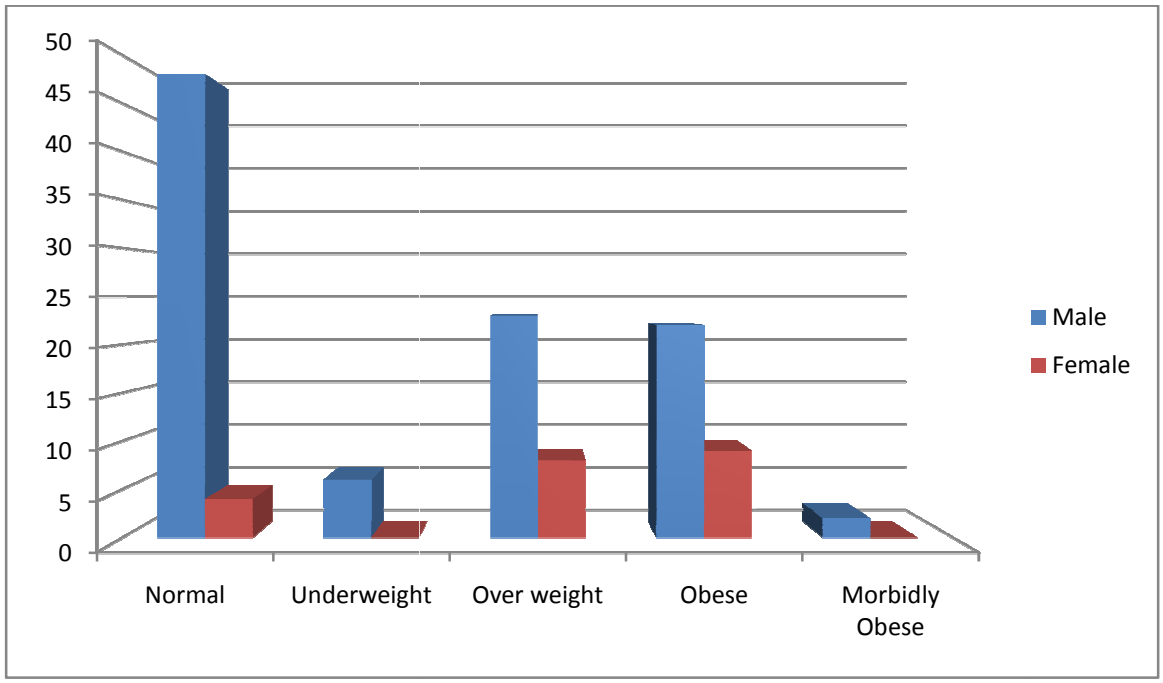


Table-2

Body Mass Index

Body Mass Index	Male		Female		Total	
	No of Patient	%	No of Patients	%	No of Patients	%
Normal	48	47.52	4	19.05	52	42.62
Under Weight	6	5.94	0	0	6	4.92
Over Weight	23	22.77	8	38.10	31	25.41
Obese	22	21.78	9	42.85	31	25.41
Morbid Obese	2	1.98	0	0	2	1.64
Total	101	100	21	100	122	100



Distribution of Body mass index of study subjects revealed that majority of them52 (42.62 %) have Normal; 6 (4.92 %) have underweight; 2 (1.64 %) had Morbid Obese; 31 (25.41 %) Over weight and 31 (25.41 %) had Obese.

Table-3

Body Mass Index

Characteristics	Male patients	Female patients	Total	Significant
	Mean ± S D	**Mean ± S D**	**Mean ± S D**	
Weight (Kg)	64.62 ± 10.27	61.00 ± 9.43	64.02 ±10.19	t=1.46 df=119 NS
Height (Cm)	165.28 ± 8.22	152.20 ± 8.08	163.12 ± 9.51	t=6.52 df=119 P<0.001
Body Mass Index (Kg/m^2)	23.71 ± 3.63	25.55 ± 3.15	24.02 ± 3.61	t=2.11 df=119 P<0.04

S D= Standard Deviation NS – Not Significant

The above table reveals that the association between body mass index and gender involvement of the sample. Mean weight total was 64.02 ±10.19 and the mean value in males was 64.62 ± 10.27 and in females was 61.00 ± 9.43. T-value reveals that there is no significant difference between weight and gender.

Comparison between gender and Height of the patients. T-value reveals that there was a statistically significant difference between male patients and female patients.

The mean score of male, female and total were 23.71 ± 3.63, 25.55 ± 3.15 and 24.02 ± 3.61. Difference between BMI scores of males and female is significant at P<0.04

TABLE-4

Control group 102 persons (Mean ± S D)

	Number	BMI	P value
Normal	21	21.5629±1.3	P<0.030
Overweight	45	24.7096±1.2	P<.003
Obese	36	31.6586±3.4	P<.005

Distribution of Body mass index of study subjects revealed that majority of them42 (41.17 %) have overweight; 21 (20.58 %) had normal; 36 (35.29 %) had Obese.

Table-5

Characteristics	Male patients	Female patients	Total	Significant
	Mean ± S D	Mean ± S D	Mean ± S D	
Waist (inch)	36.53 ± 3.58	35.75 ± 4.08	36.41 ± 3.66	t=0.88 df=119 NS
Hip (Cm)	37.95 ± 3.11	39.80 ± 3.97	38.41 ± 3.33	t=2.31 df=119 P<0.02

S D= Standard Deviation NS – Not Significant

The mean Waist of the sample was 36.41 ± 3.66 the mean waist not differed between Genders. Males had 36.53 ± 3.58 and female had 35.75 ± 4.08

The mean Hip score was significantly differed between male (37.95 ± 3.11) and female (39.80 ± 3.97) at P< 0.02.

Table-6

Blood Pressure

Characteristics	Male patients	Female patients	Total	Significant
	Mean ± S D	Mean ± S D	Mean ± S D	
Systolic Blood Pressure (mmHg)	134.55 ±23.52	137.62 ± 20.23	135.08±22.94	t=0.56 df=120 NS
Diastolic Blood Pressure (mmHg)	90.29 ± 14.72	91.90 ± 15.04	89.90±16.48	t=0.46 df=120 NS

The mean SBP of the sample was 135.08±22.94. The mean SBP score not differed significantly between males and females. The mean DBP was found to be 89.90±16.48, but did not differ significantly between males (90.29 ± 14.72) and females (91.90 ± 15.04).

Table-7

Laboratory Data

Characteristics	Male patients	Female patients	Total	Significant
	Mean ± S D	Mean ± S D	Mean ± S D	
Fasting Blood Sugar (mg/dl)	149.90 ±63.79	219.86±106.58	168.94±77.10	t=4.01 df=120 P<0.001
Cholesterol (mg/dl)	221.84 ± 59.61	223.70 ± 64.37	222.15±60.15	t=0.13 df=118 NS
Triglycerides(mg/dl)	169.57 ± 69.58	161.05 ±50.01	168.15±66.61	t=0.52 df=118 NS
LDL	143.32 ± 47.25	145.45 ±50.75	143.68±47.68	t=0.18 df=118 NS
HDL	41.93 ± 8.80	42.20 ± 11.31	41.98± 6.21	t=0.12 df=118 NS
VLDL	32.91 ± 13.14	32.15 ± 9.68	32.78±12.60	t=0.25 df=118 NS

S D= Standard Deviation NS – Not Significant

The above table reveals that association between level of Laboratory score and Gender to the patient. The Mean score on Fasting Blood Sugar mean of male was 149.90 ±63.79 and female was 219.86±106.58. T-value reveals statistically significant difference.

Though Females had meant level of Cholesterol of 223.70 ± 64.37 which is more than that the male's mean Cholesterol of 221.84 ± 59.61. t-value reveals that there is no significant difference between sex patient and cholesterol level.

The mean score on Triglycerides (mg/dl) of male is 169.57 ± 69.58 and female is 161.05 ±50.01. The males had higher score than females but the difference is not statistically significant.

The mean score on LDL female is 145.45 ±50.75and male is 143.32 ± 47.25. Females had little high score than males but the difference is not statistically significant.

Females had mean level of HDL of 42.20 ± 11.31 which is more than that the male's mean HDL score of 41.93 ± 8.80. t-value reveals that there is no significant difference between sex patient and cholesterol level.

The mean score on VLDL male is 32.91 ± 13.14 and female is 32.15 ± 9.68. The difference is not statistically significant.

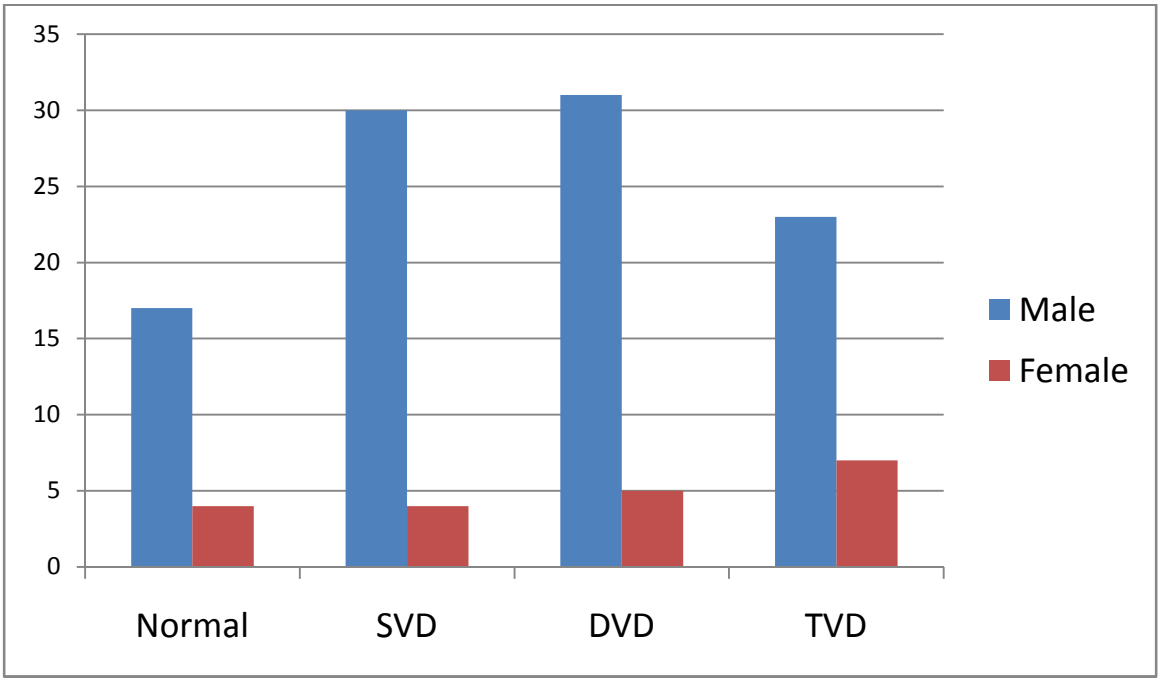
The distribution of coronary artery system among 122 patients are 9.8% (12patients) are co-dominant system, 15.5 %(19 patients) are left-dominant system, and 74.59%(91 patients) are right dominant system.63 patients are thrombolysed.

Table-8

Coronary Angiography

Coronary Angiography	Male		Female		Total	
	No of Patient	%	No of Patients	%	No of Patients	%
Normal	17	16.83	4	20.00	21	17.36
SVD	30	29.71	4	20.00	34	28.10
DVD	31	30.69	5	25.00	36	29.75
TVD	23	22.77	7	35.00	30	24.79
Total	101	100	20	100	121	100
	Chi square=1.85 df=3 Not Significant				**49.87 ± 9.13**	

The above table reveals that association between the level of Coronary information and gender status of significant patients. Among the patients 36 (29.75 %) who had Double Vessel Disease; 34 (28.10 %) who had Single Vessel Disease; 30 (24.79 %) who had Triple Vessel Disease and 21 (17.36 %) who had Normal.

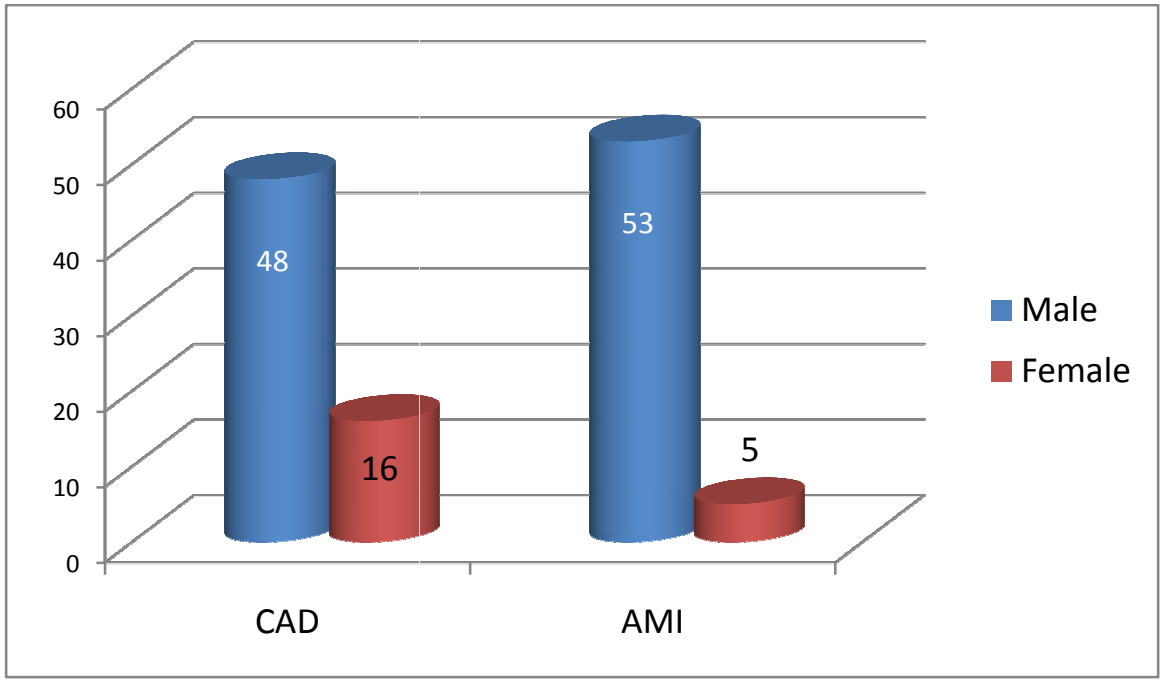


The Chi-square value reveals that there is no significant association between Coronary Disease status and the Gender.

Table-9

Diagnosis

Group	Male		Female		Total	
	No of Patient	%	No of Patients	%	No of Patients	%
CAD	48	47.52	16	76.19	64	52.46
AMI	53	52.48	5	23.81	58	47.54
Total	101	100	21	100	122	100
	Chi square= 5.73 df=1 p< 0.02 Significant					



The total sample 122 was used for this study. Males comprised 101 (82.79%) and female 21 (17.21%) of the total. Majority 64 (52.46 %) of the sample

were CAD and remaining 58 (47.54 %) were Non CAD. The distribution between sex of the CAD and Non CAD were statistically significantly differs $p < 0.002$.

Table-10

Co Morbid conditions

Group	Male		Female		Total	
	No of Patient	%	No of Patients	%	No of Patients	%
None	57	56.40	10	47.60	67	54.90
Diabetic	9	8.90	0	0	9	7.40
Hypertension	9	8.90	1	4.80	10	8.20
Previous CAD	23	22.80	4	19.00	27	22.10
DM/HT/PREVIOUS CAD	3	3.0	6	28.60	9	7.40
Total	101	100	21	100	122	100
	Chi square= 18.40 df=4 p< 0.001 Significant					

In this 122 patients 57(56.40%) patients were no co-morbid diseases, Diabetes mellitus 9 (8.90%)patients, Hypertension 9 (8.90%)patients ,previous

infarction 23(22.80%)patients, Both DM/HT/Previous Myocardial infarction3(3%) patients. Majority 64 (52.46 %) of the sample were CAD and re 58 (47.54 %) were Non CAD. The distribution of diseases in this group was statistically significantly the p value is $p < 0.001$.

Table-11

Diagnosis

Characteristics	Male patients	Female patients	Total	Significant
	Mean ± SD	Mean ± S D	Mean ± S D	
Gensini Score	25.67 ± 22.99	36.43 ± 31.82	27.54 ± 24.94	t=1.81 df=119 NS
ACC/AHA	6.41 ± 4.89	6.67 ± 5.51	6.45± 4.98	t=0.21 df=119 NS

S D= Standard Deviation NS – Not Significant

The table reveals that the association between Gender and Gensini & ACC/AHA score. The females had men level of Gensini score of 36.43 ± 31.82

which is more than the male's Gensini Score of 25.67 ± 22.99. There is no significant difference between Gender and Gensini score of the patient.

The mean score on ACC/AHA of male is 6.41 ± 4.89 and female is 6.67 ± 5.51. The difference is not statistically significant.

Table-16

Coronary Angiographic Gensini score vs. significant obstructive number of vessels

Variables	**Coronary Angiograpic vessel pattern**	**Mean ± SD**	**Significant**
Gensini	Normal	**0.70 ± 2.70**	F=23.22 p< 0.001
	Single Vessel Disease	**19.81 ± 16.01**	
	Double Vessel Disease	**36.67 ± 23.23**	
	Triple Vessel Disease	**44.15 ± 25.36**	
	Total	**27.76 ± 24.91**	

The Gensini score in normal vessel is 0.70 (0), in single vessel disease is 19.81±16.01, doube vessel disease is **36.67 ± 23, and triple vessel disease is 44.15**

± 25.36 .there is significant difference .The F=23.22, p< 0.001 .it is statistically significant.

Table-18

Gensini score vs. significant obstructive Coronary artery

Characteristics	**Normal**	**Significant obstructive coronary artery disease**	**Total**	**Significant** (normal Vs abnormal)
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	
Gensini score	0.70 ± 2.70	3318 ± 23.81	**27.53 ± 24.94**	t=6.07 df=119 p< 0.001

The above table shows statistically significant difference between normal coronary artery and significant obstructive coronary artery disease.

Table-19

Patient Characteristics

	Diagnosis	N	Mean	Std. Deviation	Std. Error Mean
BMI	CAD	63	24.45	3.57	.44
	NON CAD	58	23.54	3.61	.47
WHO RATIO	CAD	62	.9629	.20221	.02568
	NON CAD	57	.9760	.16356	.02166
IL6	CAD	64	27.1578	7.32885	.91611
	NON CAD	58	25.7310	7.61870	1.00038
CRP	CAD	64	6.5688	1.71704	.21463
	NON CAD	58	6.8017	4.68490	.61516
IMPRESSION	CAD	63	1.75	1.047	.132
	NON CAD	58	1.48	1.030	.135
GENSINI	CAD	64	27.4453	23.77125	2.97141
	NON CAD	57	27.6404	26.39750	3.49643
ACC_AHA	CAD	64	6.6719	5.36317	.67040
	NON CAD	57	6.2105	4.53847	.60114

The above table illustrates the patient characteristics between those having CAD and not having CAD. The Mean level of IL 6 in CAD patients is 27.15 nag/ml with standard deviation of 7.32. The non CAD patients have a mean IL 6 level of 25.73 nag/ml.

Table-20: Independent samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means				
	F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference
BMI	0.04	0.85	1.39	119.00	0.17	0.91	0.65
WHO RATIO	0.93	0.34	-0.39	117.00	0.70	-0.01	0.03
IL6	0.00	0.98	1.05	120.00	0.29	1.43	1.35
CRP	3.49	0.06	-0.37	120.00	0.71	-0.23	0.63
GENSINI	0.27	0.61	-0.04	119.00	0.97	-0.20	4.56
ACC_AHA	0.53	0.47	0.51	119.00	0.61	0.46	0.91

Even though the mean level of IL 6 in non CAD patients is lower than that of CAD patients, the difference was not statistically significant (p value= 0.98) as depicted in the table no.20.

Table No-21: TNF alpha levels in relation to CAD

TNF alpha levels (pg/ml)	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Normal	14	43.86	14.85	3.97	35.28	52.43	16.00	72.00
SVD	22	40.37	25.53	5.44	29.05	51.69	14.00	114.00
DVD	21	60.29	97.37	21.25	15.97	104.61	20.00	480.00
TVD	20	47.68	53.74	12.02	22.53	72.83	4.00	244.00
Total	77	48.34	59.13	6.74	34.91	61.76	4.00	480.00

The Mean TNF alpha level in normal individuals is 43.86 pg/ml in our study. The CAD patients with single vessel disease have mean level of 40.37 pg/ml is not statistically significant. The increased level of TNF alpha have been found in double vessel and triple vessel CAD which is not statistically significant. Further larger studies are needed to confirm any association between them.

Table-22: ANOVA for BMI

		Sum of Squares	df	Mean Square	F	Sig.
IL6	Between Groups	1776.873	3	592.291	14.041	.000
	Within Groups	4977.466	118	42.182		
	Total	6754.339	121			
CRP	Between Groups	61.870	3	20.623	1.768	.157
	Within Groups	1376.569	118	11.666		
	Total	1438.439	121			

The Correlation between Body mass index and Interleukin 6 level has been studied using ANOVA. There is statistically significant difference found between BMI groups and IL 6 levels in blood.

Table-23: ANOVA for CAD – Number of vessels involved

		Sum of Squares	df	Mean Square	F	Sig.
IL6	Between Groups	59.018	3	19.673	.344	.793
	Within Groups	6686.122	117	57.146		
	Total	6745.140	120			
CRP	Between Groups	18.742	3	6.247	.516	.672
	Within Groups	1417.181	117	12.113		
	Total	1435.923	120			

The above table indicates that there is no statistically significant difference between the patients who had normal coronaries or single vessel CAD or double vessel CAD or Triple vessel CAD with respect to the level of IL 6 or CRP in the blood.

DISCUSSION

This chapter deals with the detailed discussion on the findings of the study interpreted from the statistical analysis. The finding are discussed in relation to the objectives, need for the study and the related literature of the study.

TNF alpha and Interleukin 6 are one of the factor that plays a pivotal role connecting common forms of obesity and cardiovascular disease (Zhang et al.,1994).Comparison between Body mass index and TNF alpha and Interleukin 6 both control group and diseased group shows positive correlation. A notable finding is that serum TNF alpha and Interleukin 6 increases with the increase in BMI. In the case of control group there is an increase in TNF alpha and Interleukin 6 values as a function of MI. The values obtained for TNF alpha and Interleukin 6 is interestingly found to higher in CVD group when compared to control group in all categories. However the difference in TNF alpha and Interleukin 6 values obtained for CVD and control group is much pronounced in normal BMI when compared to that of obese subjects. This is a clear indication of the correlation between Interleukin 6 values and increased BMI irrespective of the disease condition.

TNF alpha and Interleukin 6 values are expected to be higher in thin subjects and lesser in obese subjects since it is known to correlate with the energy expenditure. However the computed values of TNF alpha and Interleukin 6 are much higher in obese subjects and less in thin subjects. Thus the amount of circulating TNF alpha and Interleukin 6 might be higher in obese subjects when compared to thin subjects and TNF alpha and Interleukin 6 might play a paracrine role in addition to endocrine role played in humans. The increased in TNF alpha and Interleukin 6 values in CVD subjects when compared to that of normal subjects clearly suggests that TNF alpha and Interleukin 6 acts as a proinflammatory cytokine.

This the first study to show that higher serum TNF alpha and Interleukin 6 level was associated with more severe coronary atherosclerosis confirmed by angiographic measurement with Gemini's score and ACC/AHA score.

Various studies show that there is both positive and negative correlation between serum TNF alpha and Interleukin 6 and clinical atherosclerosis. Soderberg et al found a positive association between plasma TNF alpha and Interleukin 6 level and first myocardial infarction. V Jacob Jose et al suggest that serum TNF alpha and Interleukin 6 level is elevated in patients with first acute myocardial infarction (Indian Heart J 2005; 57:39-43).Robert wolk et al suggest that TNF alpha and Interleukin 6 level in angiographically proven CAD patients had

prognostic significance. Tamer et al found that TNF alpha and Interleukin 6 levels were higher in myocardial infarction patients. However, plasma TNF alpha and Interleukin 6 levels were not associated with CV disease in the Quebec Cardiovascular study.

In our study high serum TNF alpha and Interleukin 6 level significantly present in coronary artery disease. There is a positive correlation between significant obstructive coronary artery disease predicted by Gensini score, ACC/AHA score and number of coronary vessel involvement and serum TNF alpha and Interleukin 6 level. Between the acute myocardial infarction (complete occlusive disease) and unstable angina, chronic stable angina (partial obstructive disease) the TNF alpha and Interleukin 6 level is higher in acute myocardial infarction patients. This shows that TNF alpha and Interleukin 6 is a pro-inflammatory activity. Elevated TNF alpha and Interleukin 6 levels are independent of other novel risk factors. This shows TNF alpha and Interleukin 6 plays a role in atherosclerosis. We also found that higher serum TNF alpha and Interleukin 6 level were associated with dyslipidemia, blood pressure and angiographic severity of coronary artery disease.

These findings are likely due to multiple factors such as increased sympathetic activity, enhanced platelet aggregation, increased oxidative stress, or endothelial dysfunction effects.

CONCLUSIONS

1. There is statistically significant increase in serum TNF alpha and Interleukin 6 values in patients with CAD.
2. There is also a positive correlation between BMI and Interleukin 6 which indicate proatherogenic, proinflammatory role.
3. The serum values of TNF alpha and Interleukin 6 positively correlate with the angiographic severity of CAD.
4. Further large studies needed to confirm and to determine the prognostic significance.

LIMITATIONS OF THE STUDY

Despite the statistically significant results of this study, this study examined a small number of patients. Large cohorts are required in local settings to assess the relationship of TNF alpha and Interleukin 6 levels with the severity of coronary atherosclerosis in local settings. The concentrations of serum TNF alpha and Interleukin 6 level vary according to different measuring time.

The coronary angiographic assessment is based upon luminal assessment and lacks plaque visualization. Intravascular ultrasound (IVUS) based assessment of coronary atherosclerotic burden in correlation with serum TNF alpha and Interleukin 6 levels may be an area of interest for future investigation.

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MASTER CHART

SLNO	Name	Age	Gender	Comorbid	Diagnosis	Wt	Ht	BMI	BMI_Category	wasit	HIP	WHO_RATIO	SBP	DPB	TRI	CHO	HDL	LDL	VLDL	TNF	IL6	CRP	LMCA	LAD	LCX	RCA	GENSINI	ACC_AHA
1	Aanbalagan	65	1	1	CAD	53	152	22.94	1	32	35	0.91	180	100	83	120	24	79	17	25	30.6	4.2	N	N,R90	99	99	64	12
2	Bashir	44	1	1	AWMI	57	150	25.33	3	36	35	1.02	130	99	61	142	30	100	12	38	27.5	3.3	N	50-70	70	30	18	5
3	Elumalai	49	1	3	CAD	62	172	20.96	1	30	34	0.88	110	100	135	165	34	104	27	31	13.1	4.1	N	99	N	99	40	8
4	Aruldoss	59	1	4	CAD	66	171	22.57	1	39	36	1.08	120	80	107	165	33	111	21	32	26.8	5.2	70	N	70	90	47.5	8
5	Bakthavatchalam	37	1	4	CAD	67	169	23.46	3	36	35	1.03	170	110	271	224	49	121	54	26	35.6	9.8	N	30-50,30	70,50	N	9	7
6	Arokiyaraj	57	1	2	AIWMI	53	158	21.23	1	34	37	0.92	160	100	145	224	50	145	29	56	30.7	6.8	N	30	30	30	12	3
7	dayalan	57	1	2	IWMI	66	170	22.84	1	38	39	0.97	110	70	109	142	28	94	20	31	26.2	6.2	20	N	95	90	36	13
8	Indira	51	2	2	CAD	50	166	18.14	5	31	33	0.94	130	100	156	357	46	124	28	14	19.1	4.9	N	N	N	99	0	0
9	Gunasekar	45	1	3	IWMI	50	145	23.78	3	31	38	0.82	130	90	138	327	65	234	28	41	31.8	9.8	n	n	n	n	0	0
10	ganesh	53	1	0	CAD	55	169	19.26	1	33	35	0.94	100	70	67	181	36	132	13	35	20.5	6.6	Nn	50	70	n	12.5	6
11	faizer ali	48	1	3	RAWMI	54	162	20.58	1	34	35	0.97	140	80	210	216	44	130	42	16	21.5	4.8	N	N	N	N	0	0
12	ellappan	48	1	0	RIWMI	85	170	29.41	2	37	39	0.95	110	80	160	219	44	143	32	37	49.8	9.8	N	90	N	N	20	8
13	Ekambaram	41	1	3	CAD	89	182	26.87	3	39	42	0.93	100	70	392	203	30	95	78	20	30.5	7.1	N	N	90	100	72	12
14	Dhanasekar	53	1	0	AWMI	70	176	22.60	1	36	38	0.9	160	100	256	242	49	142	51	27	23.2	3.8	n	70	90	n	14	6
15	Baskaran	23	1	3	AWMI	66	164	24.54	3	33	36	0.92	130	90	165	188	39	116	33	33	27.2	7.4	n	n	n	n	0	0
16	Arumugam	28	1	0	AWMI	54	153	23.07	3	31	34	0.84	130	80	94	172	36	117	19	25	13.5	5.4	n	n	100	50	50	6
17	arthikani	36	2	0	CAD	55	151	24.12	3	31	34	0.91	140	100	198	247	50	157	40	140	27.8	4.3	n	99	,50,90		70	19
18	Antony	59	1	0	AWMI	63	174	20.81	1	37	38	0.98	130	100	157	278	57	190	31	41	13.5	4.8	n	70-90	50=70	70	26	10
19	Alli	44	2	0	AIWMI	78	172	26.37	3	39	41	0.98	180	120	296	358	46	135	35	38	32.3	3.6	N	N	N	N	0	0
20	Ahmed basha	40	1	3	CAD	65	167	23.31	3	36	37	0.91	210	140	259	253	51	150	52	23	32.6	8.9	n	90	30	70	14	5
21	Ahmad Ullakhan	58	1	0	RAWMI	62	165	22.77	1	38	39	0.97	110	80	124	210	38	148	24	21.5	28.6	10.1	N	N	30	90	13	5

22	Abdhul Razak	45	1	0	AASMI	54	162	20.58	3	32	35	0.91	170	100	195	157	34	84	39	31	19.4	6.7	N	50,70	90	50	19.5	10
23	abdul	49	1	0	RIWMI	57	160	22.27	1	32	35	0.91	120	80	270	159	32	73	54	36	32.7	9.8	N	70	N	N	6	2
24	Arumugam	44	1	0	AWMI	75	176	24.21	3	42	40	1.05	120	80	191	205	41	126	38	38	30	4.1	N	70	N	99	22	6
25	Periyasamy	45	1	0	CAD	41	159	16.22	5	28	33	0.85	130	100	78	184	37	131	16	62	23.5	7.8	N	90	N	N	24	4
26	Pasupathi	60	1	3	RVMI	80	160	31.25	2	43	41	0.95	110	70	234	317	63	207	47	34	41.2	38	N	90	99	80	58	19
27	Panner Selvam	58	1	0	IWMI	56	170	19.38	1	34	36	0.94	140	90	315	245	49	133	63	31	22.4	6.2	N	30-70	90	99	40	13
29	Pahurdeen	65	1	0	CAD	39	160	15.23	5	29	34	0.85	180	90	128	178	38	114	26	22	17.1	4.9	70	70	70.7	90	40	12
30	Nagaraj	60	1	0	IWMI	66	180	20.37	1	38	39	0.97	170	120	187	202	40	125	37	34	13	4.2	N	N	IRR	n	33	4
31	Murugan	44	1	0	AWMI	57	150	25.33	3	36	35	1.02	130	90	61	142	30	100	12	38	27.5	3.3	n	99,70	80	30	29	9
32	Murali	60	1	0	IWMI	68	170	23.53	3	32	31	1.03	130	90	194	310	62	209	39	25	29.6	9.7	n	n	n	40	4	1
33	Vijayan	52	1	0	AWMI	51	174	16.85	5	31	34	0.91	140	90	83	292	58	217	17	39	25.4	10.1	n	99,70	80	30	43	11
34	Vijayakumari	52	2	0	IWMI	55	180	16.98	5	32	36	0.89	140	9	108	258	45	135	22	47	18.5	5.6	N	40	N	50	4	3
35	Vijay	60	1	3	CAD	71	153	30.33	4	41	43	0.95	150	90	196	193	39	115	39	20	36.2	7.8	N	70	70	80	16	6
36	Veeramuthu	50	1	0	AWMI	66	176	21.31	1	35	36	0.97	140	100	156	238	49	157	23	41	29.4	5.6	n	50	n	n	6	2
37	Thulasidoss	67	1	0	AWMI	56	169	19.61	1	36	37	0.97	160	110	88	234	45	171	18	26	25.6	6.8	n	99,100	40	40	66	10
38	Thangamani	55	1	4	AWMI	49	153	20.93	1	31	37	0.84	140	90	132	155	31	98	26	35	32.1	7.2	30	80	99	99	64	14
39	Ravichndran	54	1	1	AWMI	62	165	22.77	1	38	39	0.97	110	80	124	210	38	148	24	21.5	28.6	10.1	n	90	40	40	34	8
40	Tajum Begam	40	2	2	CAD	70	170	24.20	3	36	40	0.19	150	100	147	264	53	182	29	41.5	16.6	5.2	n	n	n	n	0	0
41	Rathakrishnan	45	1	0	IWMI	76	159	30.06	4	40	44	0.9	150	100	169	222	44	144	34	26	27	4.7	n	70,90	n	99	52	12
42	Anif	50	1	3	CAD	56	160	21.88	1	35	37	0.95	140	100	390	135	28	129	22	114	19.2	7.1	N	99	N	IRR	25	4
43	allathiya	48	2	0	RAWMI	61	176	19.69	1	33	36	0.92	120	80	399	276	55	141	80	36	24.5	6.1	N	70	N	20	5	3
44	Kesavan	42	1	0	CAD	59	170	20.42	1	36	37	0.98	140	90	160	138	20	86	32	47	22.9	6.5	N	N	N	N	0	0
45	Selvaraj	50	1	0	RIWMI	51	157	20.69	1	34	35	0.97	150	100	211	156	32	82	42	45	24.3	5.1	N	N	N	N	0	0
46	Xavier	58	1	0	CAD	73	173	24.39	3	39	41	0.95	110	70	102	140	28	92	20	244	36.7	8.5	N	50-70	30-50	40	14	6
47	Stephen	40	1	0	CAD	70	160	27.34	3	39	42	0.93	150	90	215	217	44	130	43	54	41.9	6.8	N	90	70	N	15	6
48	Shanthi	60	2	0	CAD	50	143	24.45	3	37	34	1.09	130	90	141	240	50	162	28	60	29.6	5.1	N	99	N	100	64	8
49	Shanmugam	45	1	0	AWMI	63	167	22.59	1	36	37	0.97	170	130	185	190	49	104	37	62	26.6	9.6	N	70	N	50	13	6
50	Shankar	63	1	0	CAD	57	158	22.83	1	32	36	0.89	140	90	95	147	30	98	19	32	26.7	7.5	n	90	99	20	42	9
51	S.Rajan	66	1	0	RASMI	55	166	19.96	1	33	37	0.89	110	80	92	212	43	151	18	35	24.1	3.1	n	90	n	n	24	4
52	Ravi	61	1	0	CAD	60	168	21.26	1	35	38	0.92	210	120	129	136	41	71	24	25	19.6	4.6	50	70	70	100	55	16

53	Ramu	39	1	0	CAD	86	186	24.86	3	38	40	0.95	100	80	154	196	40	125	31	27	40.2	6.7	N	100	N	N	48	4
54	Santhanam	66	1	0	CAD	54	150	24.00	3	36	40	0.9	130	90	248	321	45	168	45	57.6	23.2	7.8	50	99	90	70	47	16
55	Ravindran	48	1	0	CAD	72	171	24.62	3	37	41	0.9	110	70	192	167	34	95	38	72	48.6	7.1	N	N	N	30	2	1
56	Mary	43	2	0	CAD	78	162	29.72	2	39	42	0.93	160	100	80	152	30	106	16	38.6	39.8	10.6	n	50,50,50	30	n	11.5	4
57	Jayaraman	45	1	1	IWMI	52	165	19.10	1	32	33	0.97	130	80	207	253	51	160	42	29	14.2	3.2	n	60	100	90	74	10
58	Kanniyammal	53	2	4	CAD	64	139	33.10	2	40	41	0.98	150	100	195	173	37	97	39	102	35.6	7.2	40	80	N	N	26	6
59	KUMAR	47	1	2	CAD	60	165	22.00	1	35	36	0.97	130	80	249	176	36	90	50	65	19.1	7.1	n	n	n	n	0	0
60	Lalitha	48	2	2	CAD	70	165	25.71	3	40	44	0.91	210	140	259	253	51	150	52	23	32.6	8.9	30	70,99	50	20	51	10
61	Lalitha	60	2	1	CAD	60	151	26.30	3	40	39	1.03	160	70	243	177	36	92	49	48	16.1	6.1	N	100	N	70	53	6
62	Kousalya	41	2	3	IWMI	67	169	23.46	3	36	35	1.03	170	110	271	224	49	121	54	26	35.6	9.8	20	99	50,50	30	60	10
63	Kamakshi	47	2	0	AWMI	50	169	17.51	5	35	40	0.88	110	90	110	198	40	136	22	66	23.1	6.1	n	100	90	n	72	8
64	Ibrahim	46	1	2	AWMI	65	166	23.60	3	36	37	0.97	140	100	193	134	43.5	68	39	68	15.9	3.2	N	50	90	N	11.5	6
65	gopi	47	1	4	CAD	62	153	26.49	3	39	40	0.97	140	90	253	230	48	131	51	68	29.5	5.1	n	n	n	n	0	0
66	Ganesan	49	1	1	CAD	56	159	22.10	1	33	36	0.92	100	70	115	171	36	112	23	16.5	18.6	4.2	N	70	N	N	7	2
67	Eswaran	58	1	4	CAD	70	157	28.30	2	38	44	0.86	140	90	171	132	28	70	34	26	35.6	7.1	N	N	N	N	0	0
68	Balaraman	54	1	3	ASMI	82	174	27.10	3	42	43	0.97	130	80	157	269	55	183	31	36.5	29.6	7.5	N	N	N	N	0	0
69	Ramaiah	60	1	3	CAD	51	155	21.23	1	29	33	0.87	110	70	124	108	25	58	25	24	20.2	8.1	n	99	n	n	40	4
70	Vijaykumar	60	1	4	IWMI	67	152	29.00	2	42	46	0.91	160	90	168	177	34	110	33	65	40.2	7.8	30	90	99	100	117	13
71	Vijayakumar	48	1	4	AWMI	55	167	19.70	1	34	35	0.97	160	80	156	106	22	53	31	54.5	12.6	6.2	n	50,70	50,70	n	20	8
72	Venkatachalapat	45	1	2	IWMI	61	180	18.83	1	36	38	0.95	160	100	118	185	37	124	24	63	21.1	6.2	n	n	70,70	100	60	10
73	Varadan	49	1	3	IWMI	68	160	26.00	3	39	40	0.98	110	80	207	234	48	145	41	20	18.6	5.1	n	90	100	n	72	8
74	Thiagaraj	60	1	1	CAD	50	153	21.40	1	30	33	0.9	140	110	110	142	30	90	22	23	21.1	5.2	n	100	99	70	60	14
75	Subramani	60	1	0	AWMI	58	164	21.56	1	37	36	1.03	150	90	111	180	36	123	21	38	30.2	8.2	n	70	n	70	28	6
76	Sumathy	42	2	3	CAD	68	157	27.60	2	38	43	0.88	130	100	72	163	33	116	14	47.6	22.6	4.1	n	70	n	70	20	6
77	Ramu	57	1	0	CAD	50	145	23.78	3	31	38	0.82	130	90	138	327	65	234	28	41	31.8	9.8	n	n	n	n	0	0
78	Raji	32	1	0	ASMI	80	160	31.23	3	40	41		120	80	145	271	46	196	29	49	19.2	8.2	N	90	N	N	20	4
79	Hussain	55	1	3	CAD	70	167	25.10	3	38	36	1.06	100	70	364	240	48	119	73	4	36.7	9.9	50	70,70	70	75	80	20
80	Nagaraj	38	1	2	UA	83	171	28.42	2	41	47	0.8	120	80	120	210	26	160	24	31	37.6	7.4	N	N	N	N	0	0
81	James	52	1	0	CAD	65	167	23.30	1	30	36	0.8	150	100	150	258	32	120	20	14	17.5	3.6	N	60,99	N	30	36	9
82	Joseph	50	1	0	AASMI	58	169	20.28	1	32	35	0.8	110	70	148	270	37	203	30	41	15.8	6.7	N	50,100	N	N	51	5

83	Baskaran	67	1	2	ASMI	72	174	23.70	1	38	39	0.9	130	100	167	318	40	244	34	35	19.8	5.2	N	90,99	N	N	29	8
84	Bagvathi	55	1	0	CAD	75	162	27.98	2	41	39	1	150	90	130	158	30	102	26	16	28.6	3.9	N	90	70	90	15	6
85	Devi Bai	45	2	0	ASMI	60	172	23.47	1	33	36	0.9	120	80	150	187	35	125	30	37	25.4	4.9	N	50,70	40,40	90	35	15
86	Duraisamy	37	1	0	AWMI	72	164	26.00	2	39	40	0.9	130	80	325	393	42	286	65	20	20.9	3.1	N	N	N	N	0	0
87	Mohammed Ghouse	54	1	0	AWMI	60	161	23.00	1	37	34	1.7	110	90	174	210	50	126	34	27	17.8	3.4	N	90	40	N	14	5
88	Pappammal	47	2	0	AWMI	71	155	29.58	2	37	45	0.8	120	80	120	178	32	122	24	33	35.5	4.8	N	99	60,50	40	20	7
89	Rajendran	50	1	0	CAD	76	167	27.21	2	39	39	1	110	90	185	248	49	162	37	25	28.6	7.8	N	50	80,40	N	23	8
90	Sheik Mohideen	52	1	3	CAD	58	165	21.32	1	32	33	0.9	140	100	110	270	40	208	22	140	20.8	6.1	N	70	80	30	11	5
91	Sugumaran	38	1	0	CAD	77	163	28.95	2	38	42	0.9	100	70	125	215	50	140	25	41	32.7	6.9	N	90	70	90	20	10
92	Vijaya	51	2	0	CAD	81	167	29.03	2	37	38		160	100	140	214	46	140	28	38	30.6	7.3	A	N	N	99,	18	6
93	Velu	51	1	0	CAD	75	151	26.60	2	39	40	0.9	130	90	165	272	48	191	33	23	17.4	7.7	N	30,50	N		3	2
94	Venkatesh	50	1	4	CAD	64	152	27.00	2	33	38	0.8	140	80	130	217	41	150	26	21	23.1	6.7	N	N	N	99	80	8
95	Velu	33	1	3	CAD	70	168	24.82	1	31	34	0.9	120	80	155	193	42	118	31	31	25.7	5.3	N	N	N	30	2	2
96	Ramu	65	1	3	CAD	60	166	21.76	1	35	34	1.2	120	90	200	226	52	134	40	36	27.8	3.7	N	99	N	N	42	6
97	Sakunthala	38	2	0	CAD	56	146	26.29	2	38	43	0.9	120	80	164	264	47	232	32	38	29.3	5.9	N	100,9O	N	N	51	6
98	Pandiyan	37	1	0	CADi	62	149	27.93	2	43	40	1.7	130	80	181	328	49	243	36	62	30.2	7.9	n	90	50	20	30	6
99	Paramisivam	45	1	0	CAD	75	175	24.50	1	42	40	1.5	120	90	183	189	48	106	37	34	19.5	6.2	N	70	90	70	24.5	11
100	Rajendran	31	1	3	CAD	56	168	19.86	1	36	39	0.9	160	110	142	186	42	116	28	31	24.6	6.7	N	90	N	N	12	4
101	Rajendran	58	1	3	CAD	68	162	25.95	2	35	33	1.5	130	70	140	278	40	210	28	22	27.8	5.9	N	N	90	50	20	5
102	Mohammed	36	1	0	CAD				1				120	80						34	20.2	7.2	N	N	N	NN	0	0
103	Gopal	41	1	3	CAD	80	176	25.81	2	33	41	0.8	150	120	141	260	31	135	32	27	30.7	7.7	n	90,70	n	n	28	6
104	Kasinathan	54	1	3	CAD	66	165	24.26	1	40	43	0.9	140	100	168	235	50	151	34	57	36.2	7.5	N	100	N	50-70	52	6
105	Krishnaveni	42	2	0	RIWMI	76	168	26.95	2	42	41	1.2	160	120	116	325	48	254	23	72	32.8	8.1	N	N	N	90	8	6
106	Kumaran	52	1	0	IWMI	70	158	27.89	2	45	42	1.6	130	80	186	289	46	203	37	38	29.6	8.3	N	70	N	90	14	6
107	lelienraj	55	1	3	CAD	80	171	27.40	2	38	38	1	120	80	145	279	41	209	39	29	21.7	7.1	N	90,70	50,70	N	34	10
108	Masthan	65	1	3	CAD	80	171	27.40	2	38	38	1	120	80						102	31.7	7.1	N	N	30	N	3	1
109	Pangathachan	60	1	3	CAD	54	168	19.15	1	38	39	1.2	110	80	165	286	52	201	33	65	28.7	7.2	30	99	70,90	99	60	19
110	Raju	54	1	1	CAD	75	158	30.00	2	42	41	1.2	120	80	155	165	36	108	31	23	32.6	3.9	A	90	N	20	7	4
111	Rajendran	48	1	0	AWMI	58	146	27.03	2	35	38	0.9	120	80	140	198	42	128	28	48	26.7	5.8	N	N	N	N	0	0

112	Pazhani	35	1	0	CAD	55	166	19.93	1	34	38	0.8	120	80	186	312	48	227	37	26	19.8	7.8	N	N	N	N	0	0
113	RAMESH	42	1	3	CAD	60	145	28.57	2	40	38	1.5	130	90	182	261	47	178	36	66	28.1	4.7	N	N	N	N	0	0
114	Subramani	62	1	0	CAD	58	149	26.13	2	37	39	0.9	140	80	136	265	36	202	27	68	31.3	7	50	99,99,70	99	70,70	82	23
115	Srinivasan	50	1	0	CAD	62	163	23.31	1	41	45	0.9	110	70	145	300	49	222	29	68.5	19.7	8.2	N	50,70-90	N	N	23	8
116	Shanthi	60	2	0	RIWMI	65	149	29.29	2	40	38	1.4	150	110	120	174	40	114	24	16	32.8	7.8	N	90	90,90	N	9.5	4
117	Shahul	58	1	0	CAD	66	161	25.48	2	39	40	0.9	110	80	152	279	48	201	30	26	26.1	6.1	N	30	N	40	6.5	2
118	Santhosh	42	1	0	CAD	60	146	20.17	1	41	43	0.9	140	90	170	258	47	177	34	36	16.2	3.2	N	99	90	30	34	9
119	Murugesan	40	1	3	CAD	74	157	30.08	2	42	44	0.9	130	100	182	321	53	232	36	24	29.1	8.3	N	N	30	60,80	23	10
120	Palani	59	1	0	AIWMI	55	159	21.73	1	39	40	0.9	120	90	189	311	53	220	38	65	20.8	4.8	N	99,100	90	N	84	12
121	Natarajan	52	1	1	AASMI	55	156	22.63	1	41	40	1.2	110	80	152	242	49	163	30	54	19.8	5	N	70	70	N	12	4
122	Naveesammal	52	2	0	IWMI	65	166	23.55	1	39	42	0.8	140	120	131	248	43	179	26	46	22.3	3	N	N	N	N	0	0

PROFORMA

Name :

Age :

Sex :

Address :

CD No. :

SYMPTOMS :

No symptoms:

Chest pain:

SOB Class:

Palpitations

Risk Factors

Hypertension Diabetes Mellitus

Smoking Family History

Menopause

Past History :

Treatment History

Physical Examination

1. General Examination

2. Vital Signs

B.P

Pulse

Respiration JVP Height cm Waveform

3. Systemic Examination

CVS

Inspection / Palpation

Apex Parasternal Heave

Palpable Sounds Thrills

Auscultation

S1 S2 Murmurs

Extra Heart Sounds

Other System

RS: PA: CNS :

ECG:

ECHO :

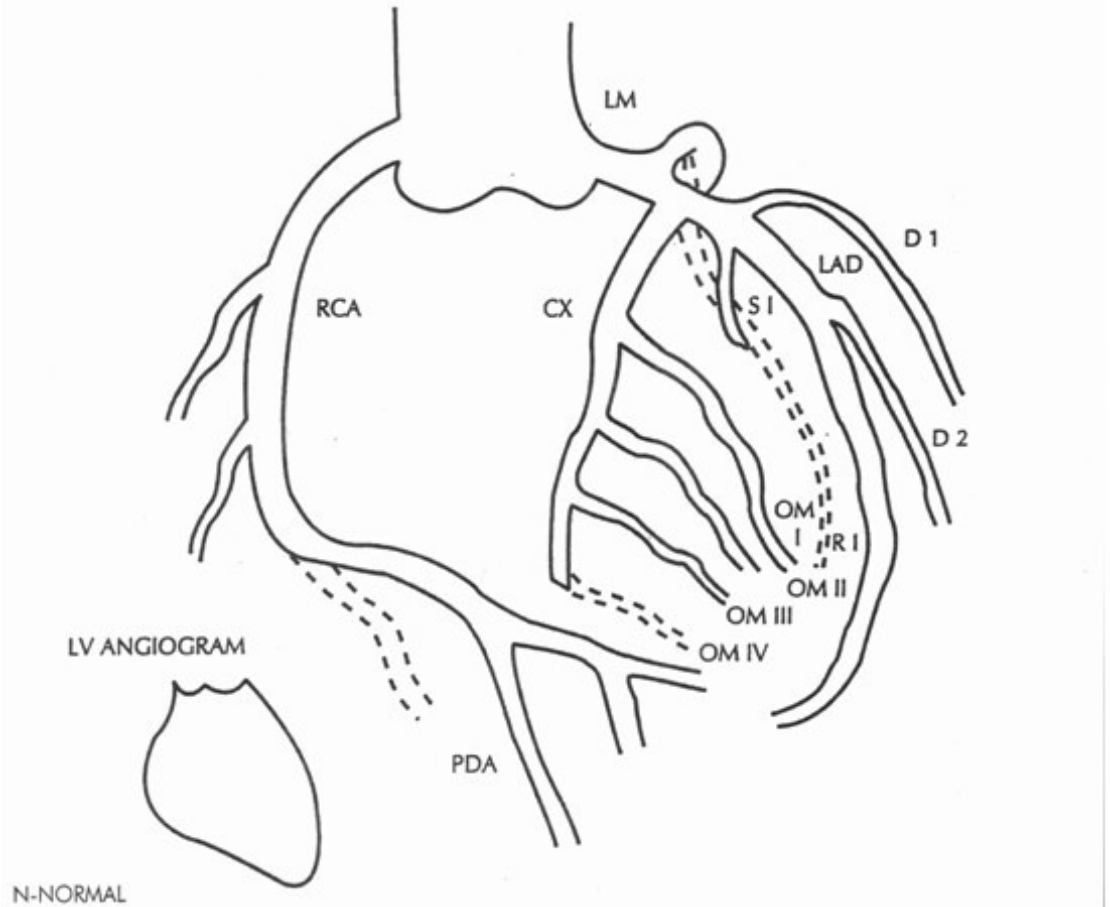
SERUM TNF-ALPHA : pg/ml

SERUM IL-6 : pg/ml

CORONARY ANGIOGRAM :

Name.....Age.....Sex.....

Cath No.....Date..... UNIT - CI / CII



N-NORMAL
A-HYPOKINESIA
B-AKINESIA
C-DYSKINESIA
D-ANEURYSM

HANSAND - ACC / AHA SCORING SYSTEM

PATIENT CONSENT FORM

STUDY TITLE :

" CORRELATION OF SERUM TNF- ALPHA AND IL-6 LEVEL WITH ANGIOGRAPHIC SEVERITY OF CORONARY ARTERY DISEASE"

Patient may check (✓) these boxes.

PARTICIPANT NAME : DATE:

AGE: SEX: I.P.NO. :

The details of the study have been provided to me in writing and explained to me in my own language. ☐

I confirm that I have understood the purpose of the above study. I have the opportunity to ask the question and all my questions and doubts have been answered to my complete satisfaction. ☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving any reason, without my legal rights being affected. ☐

I understand that investigator, the institution, regulatory authorities and the ethical committee will not need my permission to look at my health records both in respect to the current study and any further research that may be conducted in relation to it, even if I withdraw from the study. I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

I hereby consent to,undergo complete physical examination ,and diagnostic tests including hematological,biochemical,radiological and urine examinations ☐

I have been given an information sheet giving details of the study . ☐

I hereby consent to participate in the above study

Signature of the Participant

Information to Participants

Title: CORRELATION OF SERUM TNF- ALPHA AND IL-6 LEVEL WITH ANGIOGRAPHIC SEVERITY OF CORONARY ARTERY DISEASE

Principal Investigator:

Co-Investigator(if any):

Name of Participant:

Site : RGGGH& MMC, Chennai

You are invited to take part in this research/ study/procedures/tests. The information in this document is meant to help you decide whether or not to take part. Please feel free to ask if you have any queries or concerns.

What is the purpose of research?

Several pro-inflammatory cytokines, including interleukin-1, IL-6, IL-8, tumor necrosis factor-alpha, as well as anti-inflammatory cytokines IL-1 receptor antagonist and IL-10, have been identified as part of the inflammatory process of atherosclerosis.Serum levels may be elevated in patients with coronary artery disease. We therefore evaluated the relationship between the level of inflammatory cytokines and the extent and severity of CAD.We have obtained permission from the Institutional Ethics Committee.

The study design

It is a Prospective observational study

Study Procedures

The study involves evaluation of **serum TNF- alpha and IL-6 level with angiographic severity of coronary artery disease.**

Confidentiality of the information obtained from you

You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examinations, investigations, and your medical history). By signing this document, you will be allowing the research team investigators, other study personnel, sponsors, Institutional Ethics Committee and any person or agency required by law like the Drug Controller General of India to view your data, if required.

The information from this study, if published in scientific journals or presented at scientific meetings,

will not reveal your identity.

How will your decision to not participate in the study affect you?

Your decision not to participate in this research study will not affect your medical care or your relationship with the investigator or the institution. You will be taken care of and you will not loose any benefits to which you are entitled.

Can you decide to stop participating in the study once you start?

The participation in this research is purely voluntary and you have the right to withdraw from this study at any time during the course of the study without giving any reasons. However, it is advisable that you talk to the research team prior to stopping the treatment/discontinuing of procedures etc.

Signature of Investigator	Signature of Participant
date	date

ACRONYMS & ABBREVIATIONS

TNF	- Tumor necrosis Factor
IL -6	- Interleukin 6
CAD	- Coronary Artery Disease
CVD	- Cardiovascular Study
LMCA	- Left Main Coronary Artery
LAD	- Left Anterior Descending Artery
LCX	- Left Circumflex Artery
RCA	- Right Coronary Artery
OM	- Obtuse Marginal Artery
PDA	- Posterior Descending Artery
PLB	- Posterolateral Branch
S D	- Standard deviation
ANOVA	- Analysis of Variance
ACC	- American College of Cardiology
AHA	- American Heart Association

ETHICAL COMMITTEE APPROVAL LETTER

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr.A.Rudrappa,
PG in DM Cardiology,
RGGGH & MMC,
Chennai -3.

Dear Dr.A.RUDRAPPA

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled "Correlation of serum TNF – ALPHA and 12-6 level with Angiographic severity of coronary Artery Disease" No.04032013.

The following members of Ethics Committee were present in the meeting held on 05.03.2013 conducted at Madras Medical College, Chennai -3.

1. Dr.SivaKumar, MS FICS FAIS --- Chairperson
2. Prof. R. Nandhini MD -- Member Secretary
   Director, Instt. of Pharmacology ,MMC, Ch-3
3. Prof. Shyamraj MD -- Member
   Director i/c , Instt. of Biochemistry , MMC, Ch-3
4. Prof. P. Karkuzhali. MD -- Member
   Prof., Instt. of Pathology, MMC, Ch-3
5. Prof. A. Radhakrishnan MD -- Member
   Prof of Internal Medicine, MMC, Ch-3
6. Prof. S. Deivanayagam MS -- Member
   Prof of Surgery, MMC, Ch-3
7. Thiru. S. Govindsamy. BABL -- Lawyer
8. Tmt. Arnold Saulina MA MSW -- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

R Nadini

Member Secretary, Ethics Committee

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Assignment title	Medical
Author	Rudrappa Arunagiri 16101510 D.M. Cardiology
E-mail	drrudrappa1992@yahoo.com
Submission time	24-Mar-2013 02:05PM
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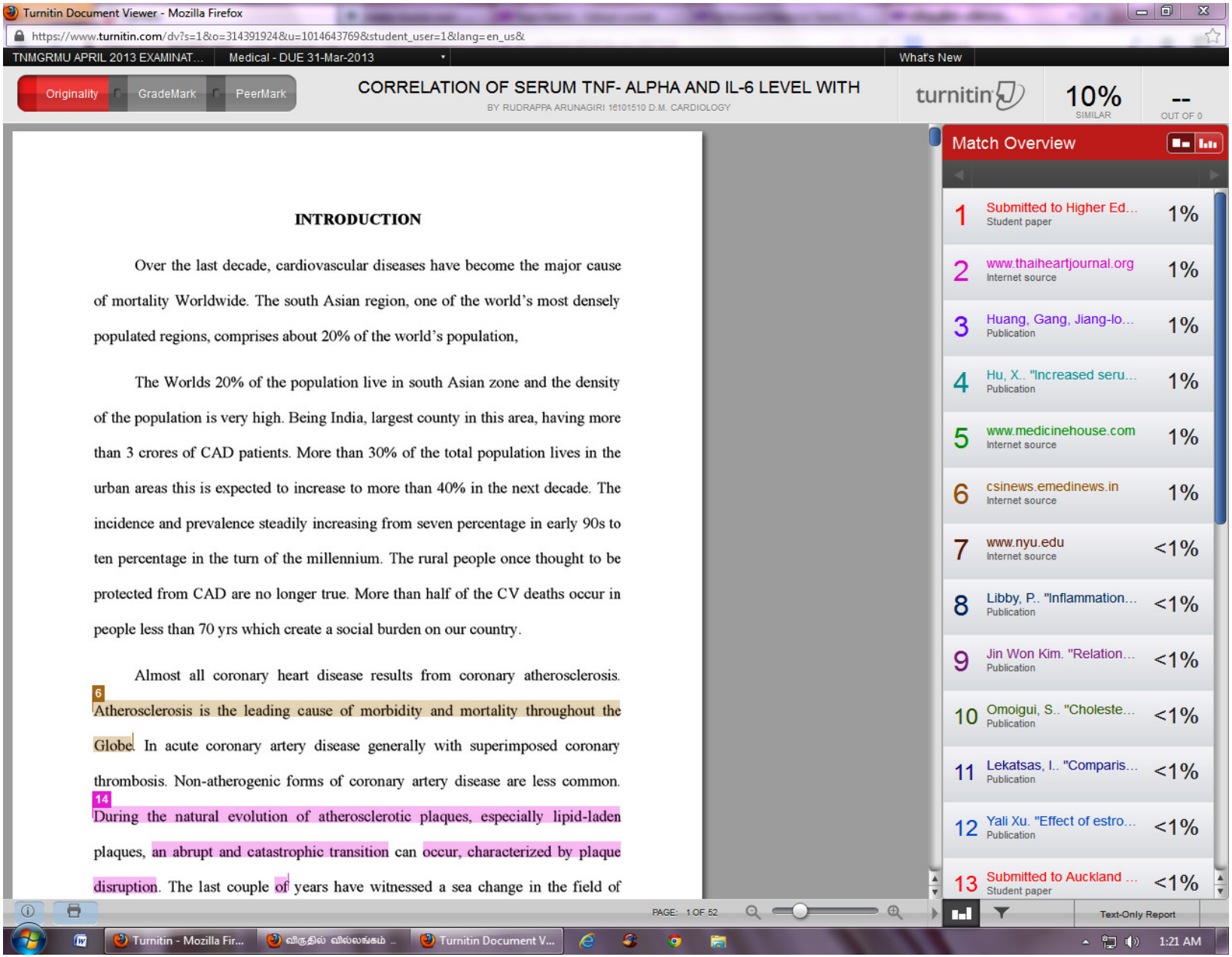
First 100 words of your submission

INTRODUCTION Over the last decade, cardiovascular diseases have become the major cause of mortality Worldwide. The south Asian region, one of the world's most densely populated regions, comprises about 20% of the world's population, The Worlds 20% of the population live in south Asian zone and the density of the population is very high. Being India, largest county in this area, having more than 3 crores of CAD patients. More than 30% of the total population lives in the urban areas this is expected to increase to more than 40% in the next decade. The incidence and prevalence steadily increasing from seven percentage in early 90s to ten percentage in the turn of the millennium. The rural...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INTRODUCTION
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The Worlds 20% of the population live in south Asian zone and the density of the population is very high. Being India, largest county in this area, having more than 3 crores of CAD patients. More than 30% of the total population lives in the urban areas this is expected to increase to more than 40% in the next decade. The incidence and prevalence steadily increasing from seven percentage in early 90s to ten percentage in the turn of the millennium. The rural people once thought to be protected from CAD are no longer true. More than half of the CV deaths occur in people less than 70 yrs which create a social burden on our country.
Almost all coronary heart disease results from coronary atherosclerosis. 6 Atherosclerosis is the leading cause of morbidity and mortality throughout the Globe. In acute coronary artery disease generally with superimposed coronary thrombosis. Non-atherogenic forms of coronary artery disease are less common. 14 During the natural evolution of atherosclerotic plaques, especially lipid-laden plaques, an abrupt and catastrophic transition can occur, characterized by plaque disruption. The last couple of years have witnessed a sea change in the field of
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